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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/869,554	06/28/2001	Anna Edman Orlefors	HO-P0221US0	4792

26271 7590 04/29/2003

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EXAMINER
SAKELARIS, SALLY A

ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 04/29/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)
	09/869,554	ORLEFORS ET AL.
	Examiner	Art Unit
	Sally A Sakelaris	1634

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 January 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-18* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

This action is in response to Applicant's amendment and response to office action, filed January 22, 2003. Claims 1-4 and 6-7 have been amended, no claims have been canceled, and claims 17 and 18 have been added. Claims 1-18 are now pending. Applicant's amendments and arguments have been thoroughly reviewed, but are not persuasive for the reasons that follow. All rejections not reiterated herein are hereby withdrawn. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action. **This action is Final.**

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

1. Claims 1-16(and now 17) are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

C. Claims 1, 5, 7, and 8 remain indefinite over the recitation of the "determining that the nucleotide base is complementary to...that is incubated". It is still unclear what these claims intend to read upon. It is unclear to which nucleotide base the claim refers, ie, every nucleotide base added, a certain single, added nucleotide base, a nucleotide base in the nucleic acid sample that is hybridized to the primer, etc. The claim should be amended to clarify which nucleotides base is under determination and exactly how it is judged.

E. Claims 2, 3, 4, 6, 9, 10, 13, 14, 15, and 16(and now 17) remain indefinite over the recitation of "required number of times" in step (iv). The term "required" is not defined by the

claim, the specification does not provide a standard for ascertaining the requisite degree and one of ordinary skill in the art would not be reasonably appraised of the scope of the invention. There is no fixed definition in the art for what constitutes "required". It is unclear by whom, or for what purpose the requirement is meant. The claim should be amended to clarify why the repetition of steps (ii) and (iii) would be a required step.

H. Claims 3, 9, 13, and 14(and now 17) remain indefinite as step (ii) refers to hybridizing DNA or primer to "predetermined areas." It is unclear how a hybridization step would occur between the nucleic acids of the DNA and primer and the surface of a microfluidic device. The claims should be amended to clarify exactly to what the DNA or primer would be hybridizing.

-----THE FOLLOWING IS A NEW GROUND OF REJECTION-----

2. Claims 1-16(and now 17) are further rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. Claims 2, 4, 6, 10, 11, 12, 15, and 16 are indefinite. Claims 2 and 4 do not clearly relay the role of the "primer DNA" in the reaction area and surface of the microfluidic device respectively. It is not clear whether the primer DNA is hybridized to the surface of the device or instead if just the "primer DNA" is hybridized to the single stranded sample DNA which is in turn hybridized to the surface of the microfluidic device. Claim 2 is further indefinite as its reference to both "primer DNA" and "DNA primers" make the claim's intended use of the

primer DNA unclear. Applicant should amend the claims to clarify the role of the primer DNA in the one or more reaction areas of the microfluidic device.

-----THE FOLLOWING ARE REITERATED REJECTIONS-----

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

3. Claims 1, 3, 5, 7, 9, and 13(and now 17) are rejected under 35 U.S.C. 102(b) as being unpatentable over Ronaghi et al.(Anal. Biochemistry, 1996).

Interpreting claim 1's recitation of a "microfluidic device" to mean any device which is suitable to operate with liquids on a microliter scale, Ronaghi et al. teaches the methods of such a device. Ronaghi et al. teach a method of determining a nucleotide base in a nucleic acid sample comprising the steps of:

(i) Incubating the nucleic acid sample with about 5 pmol primer, DNA polymerase, and a deoxynucleotide triphosphate, whose addition causes a release of pyrophosphate(Page 85(10)).

(ii) measuring the pyrophosphate released in step (i)(Page 85); and

(iii) determining that the nucleotide base is complementary to said deoxynucleotide triphosphate that is incubated in step (i)by measuring which nucleotide caused the release of pyrophosphate in step (ii), wherein this release is detected by light emitted from a luciferin luciferase reaction and is performed in real time(Page 85). Furthermore, as suggested by

Ronaghi, his device "would provide a flow system, with small volumes, high speed and low cost"(Page 88), thus fitting one definition of "microfluidic device."

With respect to Claims 3, 9, and 13(and now 17) Ronaghi et al. further teach a method of determining a nucleotide base in a nucleic acid sample comprising the steps of:

(i) attaching 0.8 pmol(Ronaghi, Fig. 5) of a single-stranded sample DNA by way of streptavidin-coated super paramagnetic beads within the surface of a solid support;

(ii) hybridizing small amounts of primer respectively to the same surface of a solid support;

(iii) adding the four different nucleotides to the immobilized template hybridized to a primer. The PPi released in the DNA polymerase-catalyzed reaction is detected by the ATP sulfurylase- and luciferase-catalyzed reactions in real time. The height of the signal is proportional to the number of bases which have been incorporated.

(iv) repeating step (iii) as required to construct a DNA sequence for the elongated primers, and hence for portions of the sample DNA(Fig.1, 85).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. Claims 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, and 16(and now, **17 and 18**) are rejected under 35 U.S.C. 103(a) as being unpatentable over Ronaghi et al.(Anal. Biochemistry, 1996) in view of Mian et al.(US Patent 6,319,469 B1).

With respect to claims 1, 4, 5, 10 and 15 Ronaghi et al. teach a method of identifying the sequence of a portion of sample DNA by determining a nucleotide base pair in a nucleic acid sample comprising the steps of:

(i) Incubating the nucleic acid sample with about 0.8 pmol primer, DNA polymerase, and a deoxynucleotide triphosphate(Page 88, Fig. 5).

(ii) measuring the pyrophosphate released in step (i)(Page 85); and

(iii) determining that the nucleotide base is complementary to said deoxynucleotide triphosphate that is incubated in step (i) by measuring which nucleotide caused the release of pyrophospate in step (ii), wherein this release is detected by light emitted from a luciferin luciferase reaction and is performed in real time(Page 85).

With respect to Claims 2 and 11, Ronaghi et al. teach a method for identifying the sequence of a portion of sample DNA comprising the steps of:

(i) immobilizing a double stranded DNA, comprising one strand of sample DNA and one strand of primer DNA onto a solid support;

(ii) adding the four different nucleotides to the immobilized template hybridized to a primer. The PPi released in the DNA polymerase-catalyzed reaction is detected by the ATP sulfurylase- and luciferase-catalyzed reactions in real time. The height of the signal is proportional to the number of bases which have been incorporated.(Page 85)

With respect to Claims 3, 9, and 13(and now 17) Ronaghi et al. further teach a method of determining a nucleotide base in a nucleic acid sample comprising the steps of:

(i) attaching 0.8 pmol(Ronaghi, Fig. 5) of a single-stranded DNA by way of streptavidin-coated super paramagnetic beads on the surface of a solid support;

(ii) hybridizing small amounts of primer respectively to the same surface of a solid support;

(iii) adding the four different nucleotides to the immobilized template hybridized to a primer. The PPi released in the DNA polymerase-catalyzed reaction is detected by the ATP sulfurylase- and luciferase-catalyzed reactions in real time. The height of the signal is proportional to the number of bases which have been incorporated.

(iv) repeating step (iii) as required to construct a DNA sequence for the elongated primers, and hence for portions of the sample DNA(Fig.1, 85).

With respect to Claims 1 and 8 (interpreting the "microfluidic device" as one of the preferred embodiments of the specification), Ronaghi et al. does not teach a method for identifying the sequence of a portion of sample DNA wherein the steps are performed in a microfluidic device that is a disk and the fluids are moved by centripetal force, such as that which is referred to on page 5, line 32 of the current specification. With respect to Claims 2 and 12 Ronaghi et al. does not teach forming immobilized double stranded DNA on one or more reaction areas in a microchannel structure of a microfluidic device that is a disk and the fluids are moved by centripetal force. With respect to Claims 3 and 14 Ronaghi et al. do not teach attaching DNA to a microfluidic device that is a disk and moving fluids by centripetal force.

With respect to Claims 4 and 16, Ronaghi et al. does not teach adding sample DNA to a microfluidic device or moving the sample to a reaction chamber on the microfluidic device that is a disk and the fluids are moved by centripetal force. With respect to Claim 6, Ronaghi et al. does not teach a detection step that involves labeled terminator. With respect to new claim 18 Ronaghi et al. does not teach forming immobilized double stranded DNA on one or more reaction areas in a microchannel structure of a microfluidic device, or the adding of fluorescently labeled dideoxynucleotides and a DNA polymerase to each of said one or more reaction areas so that extension of primer occurs as a result from complementarity of the added dideoxynucleotides with the strand of sample DNA that is part of the immobilized double stranded DNA.

However, with respect to Claims 1 and 8, 3 and 14, 4 and 16, and 2 and 12, 6, and new claim 18 Mian et al. teach performing the previously taught methods of Ronaghi inside a microfluidic device. In consideration of claims 1, 3, 4, 8, 13, and 16(and now 17)Mian et al. teach performing the steps of forming immobilized double stranded DNA on a reaction area in a microfluidic device, attaching or hybridizing single stranded DNA, and plainly adding sample DNA to a predetermined area on a microfluidic device that is a disc and whose fluids can be moved to various chambers. Furthermore, the Mian reference adds teachings of a disc-shaped, microfluidic device that causes fluid movement through the use of centripetal force. The reference even further teaches that such methods and apparatus are advantageous as they fill the need in the art for a simple, flexible, reliable, rapid, and economical microanalytic and microsynthetic reaction platform for performing biological, biochemical, and chemical analyses and syntheses that can move nanoliter to microliter amounts of fluids. The reference provides

that the invention also advantageously combines "wet" chemistry capabilities with information processing, storing and manipulating ability. The addition of the disc-shaped microfluidic device that exploits centripetal force, to this method for sequence identification, conferred the ability to properly mix reaction components, remove reaction side products, and isolate desired reaction products and intermediates.(Col 3, lines 5-25)(Col 48, line 67) Furthermore, with respect to claims 2 and 12, Mian et al. add the teaching of forming DNA to a "microchannel structure" within the microfluidic device. The reference teaches that; the unique disc shape and ability to move nanoliter to microliter amounts of fluid, including reagents and reactants, at rapid rates to effect the proper mixing of reaction components through the use of microchannel structures and centripetal force, provides a remedy for the many deficiencies of the status quo. The use of microchannels, functioning to separate micro-amounts of fluid reagents, and centripetal force, to move fluids into and out of reaction chambers, facilitates high-throughput analysis for both genome sequencing and routine clinical applications that require such multiplexability.

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have conducted the method of Ronaghi et al. in view of the methods of Mian et al. by incorporating a disc-shaped microfluidic device with microchannels and caused fluid flow through the use of centripetal force in order to have achieved the expected benefit of providing a method that could be used for the automation of larger sequencing projects and for the provision of a "high-throughput system."

With respect to Claim 6 and new claim 18, Mian teaches a detection step that involves a labeled terminator (Col 49, lines 5-10). Mian et al. teach a method wherein the detection step comprises the DNA being transferred into a mixing chamber containing terminator solution by

spinning the disk. Terminator solution typically comprises 100nl of a solution containing 5 picomoles of each deoxynucleotide and 0.5 picomoles of one dideoxynucleotide covalently linked to a fluorescent label. The set of dideoxynucleotide-terminated DNA fragments comprising the reaction mixture is then separated by capillary electrophoresis and the sequence of the fragments determined by laser-induced fluorescence detection. The reference further teaches that this mode of detection ie, discs comprising a multiplicity of these synthetic arrays with fluorescent labels, permits the simultaneous synthesis of a plurality of dideoxynucleotide-terminated oligonucleotides and therefore applicable in high throughput analysis of sequencing data or clinical approaches. With respect to claim 6, the reference teaches the use of a terminator solution containing a dideoxynucleotide covalently-linked to a fluorescent label in Example 7, Col. 49. With respect to new claim 18 Mian et al. teach, in addition to the aforementioned, fluorescently labeled dideoxynucleotide of Example 7, Example 3 which includes the incorporation of fluorescently labeled DNA to one or more reaction areas so that extension of primer occurs as a result from complementarity of the added dideoxynucleotides with the strand of sample DNA that is part of the immobilized double stranded DNA.

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have conducted the method of Ronaghi et al. in view of the methods of Mian et al. and to have added a labeled terminator and fluorescently labeled dideoxynucleotides, in order to have achieved the benefit of providing a method that, would permit the simultaneous synthesis of a plurality of fluorescently labeled dideoxynucleotide-terminated oligonucleotides and therefore applicable in high throughput analysis of sequencing data or clinical approaches.

5. ***Response to Arguments***

I. ***Claim Rejections - 35 USC § 112 2nd ¶***, applicants state that the previous grounds of rejection have been obviated by the amendments to the claims. However, some of the rejections are maintained and a new rejection is presented as the amendment and response do not address subject matter of previous rejections "C" "E" or "H" or the new rejection above concerning "primer DNA".

II. ***Claim Rejections 35 USC § 102(b),*** applicants traverse all rejections based on Ronaghi et al, as they believe the examiner erroneously construes the meaning of "microfluidic device" to mean any suitable device which holds liquids on a microliter scale. Applicants contend that it is well known to those of skill in the art that the term refers to a device in which there is a transport of liquid. Applicant is reminded that limitations present in the specification cannot be read into the claims. As a result, such an interpretation of the term "microfluidic device" is deemed warranted by the examiner and the rejection is maintained. In response to applicant's comment regarding the Examiner's statement on Page 9 of the action, applicant is reminded that each rejection is separate and should be evaluated as such. The examiner's comments on page 9 were in reference to the 103 obvious rejection of claims 1-16, and included different limitations than those present in claims 1, 3, 5, 7, 9, and 13 which were rejected under 102(b). Applicant has taken the examiner's statement at page 9 out of context. The presently rejected claims 1, 3, 5, 7, 9, and 13 do not include these limitations that the microfluidic device "is a disk and the fluids are moved by centripetal force" which is only required in claims 8, 12, 14, and 16.

III. ***Claim Rejections - 35 USC § 103,*** applicants traverse all rejections based on Ronaghi et al. in view of Mian et al. on the grounds that they believe neither reference alone or in

combination teaches or suggests the present invention. As reiterated above, the examiner maintains her rejections as she believes all limitations(specifically, sequencing technique and the accomplishment of the same advantages) of the present claims are obvious by the combination of these two references. With respect to Applicant's arguments concerning the relied upon reference's teachings of sequencing, as enumerated in the above 102 and 103 rejections, teach every step involved in the claimed sequencing procedure as either being anticipated or obvious respectively. The references provide for "incubating the nucleic acid sample with a primer, DNA polymerase, and a deoxynucleotide triphosphate, deoxynucleotide triphosphate analogue **or** a dideoxynucleotide triphosphate, which releases pyrophosphate when added to the primer by action of DNA polymerase" for example.

Applicant is further reminded that the motivation to combine the two references can be found by a person of ordinary skill in the art. The examiner used the first reference's(Ronaghi et al) suggestion that; "For instance by immobilization of the DNA template in a capillary the template loss observed for the paramagnetic beads could be avoided. In addition, in a flow system, with small volumes, high speed and low cost can be obtained"(Page 88) as the motivation for combining the first method of Ronaghi et al. with the second reference of Mian et al. having such a recommended "flow system, with small volumes" for the expected benefit of providing "high speed and low cost". Therefore, a statement that modifications of the prior art to meet the claimed invention would have in fact been "well within the ordinary skill of the art at the time the claimed invention was made".

In response to applicant's argument on page 9 concerning the many advantages and avoidance of drawbacks that result through the use of their device, the examiner rebuts that not

only are any of these parameters in the claims, but also that these same advantages exist in the combination of Ronaghi et al and Mian et al references. If applicant believes that the novelty of their invention lies in the "removal of excess reagents and soluble products from a growing immobilized primer to decrease the risk of artifacts", then they must include these limitation in the claims. The same is true for their argument concerning the device's ability to function without diminished reliability without apyrase and with minimized reagents.

6. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communication from the examiner should be directed to Sally Sakelaris whose telephone number is (703) 306-0284. The examiner can normally be reached on Monday-Friday from 8:00AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W.Gary Jones, can be reached on (703)308-1152. The fax number for the Technology Center is (703)305-3014 or (703)305-4242.

Any inquiry of a general nature or relating to the status of this application should be directed to Chantae Dessau whose telephone number is (703)605-1237.

4/24/03

Sally Sakelaris

CARLA J. MYERS
PRIMARY EXAMINER